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REVIEW ARTICLE

Clinical applications of PET using C-11/F-18-choline in brain tumours: a systematic review

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Abstract
Purpose The purpose of this study is to conduct a systematic review of the published data about the current indications in clinical practice for the use of positron emission tomography (PET) or PET/computed tomography (PET/CT) using either Carbon-11 (^{11}C) or Fluorine-18 (^{18}F) choline tracer in brain tumours.
Methods A comprehensive literature search of PubMed until April 30, 2016 with the Mesh terms: ''positron emission tomography'', ''choline'', and ''brain neoplasm'' was first performed. On a second step, the references of the retrieved articles were also screened, adding any relevant publications about the subject.
Results A total of 15 articles corresponding to 453 patients with brain lesions (mostly gliomas) were included for the analysis, successfully imaging brain tumours for the following indications: diagnosis and tumour characterisation; biopsy guide; treatment planning; differential diagnosis of recurrence or radiation necrosis; and therapy response assessment and prognosis. In addition, other brain lesions have been imaged by PET choline, such as meningiomas and metastasis. PET or PET/CT with radiolabelled choline must be considered as an emerging procedure for the evaluation of brain tumours. Since choline has a low physiological uptake, it provides precise images with a very good tumour-to-background ratio, especially in lesions with disruption of the blood–brain barrier.
Conclusions Even though the small population and heterogeneity of analyzed studies precluded performing a meta-analysis, the exposed results in this review support the use of choline in the aforementioned indications based on its availability, but larger studies are needed to better validate its use.

Keywords Positron emission tomography · Systematic review · Choline · Fluorine-18 (^{18}F) · Carbon-11 (^{11}C) · Brain tumours

Introduction

Brain tumours are a challenging clinical issue. The cause of most brain tumours is unknown, and despite intensive therapeutic efforts, the majority of these neoplasms remain incurable [1]. Routine diagnostic and treatment monitoring of brain tumours is usually based on contrast-enhanced magnetic resonance imaging (MRI). However, after therapeutic interventions, its capacity to differentiate tumour from non-specific treatment changes can be limited [2]; this is the main reason for the increasing use of molecular imaging in neuro-oncology. It includes advanced sequences of MRI (aMRI) as diffusion-weighted imaging, diffusion tensor imaging, perfusion-weighted imaging (PWI), and proton MR spectroscopy (MRS) [3, 4], and also nuclear medicine techniques [5, 6].

Positron emission tomography (PET) is one of the most promising techniques for imaging specific processes, providing relevant additional information on tumour metabolism and helping clinical decision-making. PET scans are, especially, useful in the cases of inconclusive MRI findings [1]. They can provide relevant information prior to

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treatment, such as, estimating tumour aggressiveness, performing image-guided biopsy [6], and, perhaps, most importantly in treated patients, when helping to distinguish tumour progression from structural changes secondary to treatment [7]; the last case is the main clinical context, in which the usefulness of ^{18}F-fluorocholine (FCH) arises [8].

PET imaging with ^{18}F-fluorodeoxyglucose (FDG) plays a significant role in the evaluation of tumours; however, it is limited in the evaluation of areas with high physiologic uptake, for example, the brain [9]. Therefore, other PET tracers have been investigated, such as aminoacid analogues, which are particularly attractive for imaging brain tumours, because of the high uptake in tumour tissue and low uptake in normal brain, yielding a greater tumour-to-normal-brain ratio (T/N) [9].The best-studied amino acid tracer is ^{11}C-methionine (MET) [10, 11].

The major drawback of ^{11}C-methionine is the very short half-life of the isotope (20 min) which limits its use to PET centres that have on-site cyclotron facilities. Because of practical issues, the need for longer lived isotopes has led to the elaboration of the ^{18}F-labelled derivatives [12]. Specific PET fluorinated tracers are currently being developed. The best documented for brain imaging are labelled aminoacids, leading even to their recent inclusion in the guidelines of the Response Assessment in Neuro-Oncology working group and European Association for Neuro-Oncology [13]. The ^{18}F-ethyL-tyrosine (FET), a recently introduced amino acid PET tracer for the diagnosis of brain tumours, has been shown to exhibit a similar diagnostic potential to MET; however, it is not available in all countries or centres [14]. On the contrary, ^{18}F-Fluorocholine (FCH) has widely been investigated as a diagnostic tool in prostate cancer restaging [15], therefore, it is largely available in the majority of PET centres [16].

We aimed to review the mechanisms that justify its usefulness and the clinical applications of PET choline (PET-CHO) for brain tumours in the clinical practice.

Rationale

Choline-based PET tracers rest on the research of biochemical processes of membrane synthesis. All cells use choline, a quaternary ammonium nutrient, as a precursor for the biosynthesis of phospholipids, which are essential components of all membranes. Choline is necessary for phospholipid synthesis in cell membranes, transmembrane signalling, metabolism, and transport of lipid cholesterol (in all cells), and is also a precursor for the synthesis of the neurotransmitter, acetylcholine [17]. Choline is an extrinsic metabolic substrate that enters the cell via specific low affinity, sodium-independent transporters [18]. Within the cell, choline is phosphorylated by the enzyme choline kinase (CK), and it is incorporated into phosphatidylcholine (lecithin), the major cell membrane constituent [18].

Rapidly proliferating tumours increase membrane/fatty acid requirements, which may account for the higher phospholipid metabolite levels in cancer tissue than in healthy tissues [19]; therefore, malignant transformation cells are associated with an increase in cellular transport and choline phosphorylation [20], elevated CK activity [21], and lipogenesis [22]. Furthermore, it is also known that rapidly proliferating tumours contain large amounts of phospholipids, particularly lecithin [23]. All this supports the use of choline as an oncological probe. It was predicted that in tumour cells that exhibit an enhanced proliferative activity, the uptake of radiolabelled choline would keep up with the increased demands for the synthesis of phospholipids. Alternatively, in slowly proliferating tumours, high phospholipid metabolite levels may be more related to alterations in choline transport, incorporation, and utilization [24, 25]. Interestingly, malignant transformation is associated with an increase in the cellular transport and phosphorylation of choline as well as an increase in the expression of CK [20, 21, 26].

Choline can be labelled either with ^{11}C (^{11}C-Choline) or ^{18}F (^{18}F-fluorocholine, FCH). As a tracer, ^{11}C-Choline is biochemically indistinguishable from natural choline and is rapidly oxidized to result radiolabelled derivatives of betaine [27]. As mentioned above, the major drawback of ^{11}C-choline is the very short half-life, which stresses the practical need for longer lived isotopes, such as ^{18}F-labelled derivatives. When ^{18}F-fluorocholine was proposed for diagnostic use, there was concern that the introduction of a very electronegative atom like ^{18}F into the molecule would deform the structure of choline and change its physiological properties.

In 1997, Hara et al. [28] developed and synthesized the first ^{18}F-labelled choline analogue: 2-fluoroethyl-dimethyl-2-oxyethylammonium choline (FEC). On the basis of structural similarity, DeGrado et al. [29] speculated that ^{18}F-fluoromethylated choline (FCH) would mimic choline transport and metabolism more closely than that of the FEC. In their study, DeGrado et al. [30] evaluated the biologic acceptance for phosphorylation by CK and the uptake by cultured PC-3 human prostate cancer cells of different choline analogue tracers synthesized through ^{18}F-fluoroalkylation reactions: FCH, FEC, ^{18}F-fluoromethyl-methylethyl-2-hydroxyethylammonium (FMEC), and ^{18}F-fluoropropyl-dimethyl-2-hydroxyethylammonium (FPC). FCH and FMEC revealed in vitro phosphorylation by CK that was similar to that of choline, whereas rates of phosphorylation of FEC and FPC were significantly lower. Accumulations of FCH, CH, and FPC in cultured PC-3 cancer cells were comparable, whereas uptake of FEC was

approximately one-fifth that of FCH. They concluded that the fluoromethylcholine analogue FCH may serve as a probe of choline uptake and phosphorylation in cancer cells, whereas FEC and FPC analogues appear to have relatively poorer biologic compatibility. In summary, in vitro studies have clearly documented that these fluorinated choline analogues are good substrates for the enzyme choline kinase, but not for the enzymes involved in the oxidation of choline. As a result, no fluorinated derivatives of betaine have been observed. The bio-distribution of both FCH and FEC is very similar to that of choline, except for their very rapid urinary excretion. This study comparing these choline analogues has shown that endogenous choline transport and metabolism are more closely mimicked by FCH than by FEC, resulting in physiological processing closer to that of choline for the fluoromethylated analogue [30].This is important, because the phosphorylation step is thought to be essential for PET imaging and metabolic retention of the tracer within the tumour, whereas non-metabolizable fluorinated analogues that are not a substrate for the enzyme CK will not be retained [31]. Even though a direct comparison study has not been performed yet and that small differences have been observed in the bio-distribution of ^{11}C-Choline, FEC, and FCH [32, 51], authors agree that, in terms of clinical applications, the diagnostic accuracy is similar for the three tracers [32, 33].

^{18}F-Fluorocholine is more widely available that ^{11}C-choline, because of the 109.8 min half-life of the isotope. Choline PET/CT (PET-CHO) has proven to be a good alternative in the diagnosis of slow-growing and well-differentiated cancer types, for which FDG can be falsely negative, such as prostate cancer [34], hepatocarcinoma [15, 35], and multiple myeloma [36]. As a major advantage of fluorinated tracers constitutes its large availability, ^{18}F-Fluorocholine expanded use has also been emphasized in a recent review [16].

In the brain, animal studies showed that ^{18}F-Fluorocholine is also taken up by glioma cells with a high tumour-to-background ratio [37, 38]. The brain homeostasis is achieved by the presence of the blood–brain barrier (BBB), a physiological microvascular unit that is selectively permeable, according to the nature of the substance (passive transport for lipophilic compounds). Choline is an essential nutrient, required for the synthesis of phospholipids and acetylcholine. It crosses the BBB through an active carrier-mediated transport (as well as glucose and aminoacids), but also by a specific high-affinity choline transporter (BBBCHT) which is a sodium-independent membrane transporter [39]. The most important works about FCH uptake and kinetics have been developed by the group of Spaeth and Wyss [37, 38, 40]. These authors [40], evaluated the effect of BBB disruption alone on uptake of ^{18}F-fluoroethyl-L-tyrosine (FET) and FCH. For this purpose, FET and FCH accumulation was determined in cryolesions, which are characterized by a heavily disrupted BBB but, in contrast to radiation injury, absence of inflammatory cells. They found that the degree of uptake of FCH and FDG correlated with the density of macrophages. In cryolesions, FET uptake was similar to that in radiation lesions, and FCH uptake was significantly reduced and concluded that FET uptake is most likely due to a disruption of the blood–brain barrier alone, whereas FCH is additionally trapped by macrophages. Uptake of both tracers in the radiation injuries is generally lower than the published uptake in tumours, suggesting that FET and FCH are promising tracers for separating radiation necrosis from tumour recurrence.

This group in subsequent studies [37, 38] showed that microvascular density influences the uptake of FCH, but not of FET or FDG [37] and compared several potential PET tracers, including FCH, FET, and FDG for glioma imaging. Although FDG and FET have higher uptake in glioma than FCH, they also represent higher uptake in surrounding normal cerebral tissues. The ratio between glioma and normal tissue was 3.77 for FCH, 2.58 for FET, and 1.98 for FDG, and concluded that of the three investigated ^{18}F tracers, FCH, and FET showed a better uptake pattern in glioma than FDG [38]. In this study, it was proposed to correlate the uptake of FCH, FET, and FDG with the degree of neoangiogenesis, as in a previous study, they showed that microvascular density influences the uptake of FCH, but not of FET or FDG, and shows that the pattern of FCH and FET uptake seems to correspond better with neoangiogenesis than did the pattern of FDG uptake.

The specific aspects of the use of FCH in the clinical setting of brain tumours in humans were reported by the group of Mertens et al., describing the distribution patterns in normal subjects and in the presence of disease [41] and the optimal timing for imaging [42].

In brain tumour imaging, the use of ^{18}F-Fluorocholine PET/CT offers the advantages of rapid blood clearance and low uptake of radiotracer in normal parenchyma and specific tumour uptake [30]. DeGrado et al. [29], in their preliminary imaging studies, showed an excellent feasibility of FCH-PET in brain tumour, specifically in a patient with biopsy proven recurrent anaplastic astrocytoma, probably due to the low concentration of ^{18}F-Fluorocholine uptake in the normal cerebral cortex, allowing an excellent delineation of the tumour from normal brain. Hara et al. [43] found that ^{18}F-Fluorocholine rather than for ^{11}C-Choline was suitable for imaging gliomas, although image quality and tumour-to-normal-brain tissue ratios (T/N) were slightly higher for ^{18}F-Fluorocholine than for ^{11}C-Choline. The shorter positron range of ^{18}F probably explains the better image quality with ^{18}F-Fluorocholine in terms of spatial resolution.

Evidence for clinical use

The clinical use of choline PET/CT (PET-CHO) in neuro-oncology dates from less than 20 years ago, which explains why it is not yet well known. Therefore, does the PET-CHO provide additional valuable information than standard imaging for the management of patients with brain tumours?

This systematic review of the literature addresses the usual clinical problems in neuro-oncology: primary diagnosis and tumour characterization; guide for biopsy; radiation treatment planning; differential diagnosis of tumour recurrence from post-treatment changes; and treatment response assessment and prognosis. Unfortunately, the available evidence of PET-CHO is very heterogeneous: two similar but not identical radiotracers (^{11}C-choline and ^{18}F-choline); patients selected from more than one indication in the same study; mixed series with different types of brain tumours; not similar clinical settings (naïve and treated); and using two different gold standards for comparison (histopathological analysis or follow-up). Then, the aforementioned issues prevented proper meta-analysis due to significant heterogeneity.

The aim of this work is to review and define the PET choline applications for brain tumours in the clinical practice.

Methods

A comprehensive computer literature search of the PubMed database was carried out to find relevant peer-reviewed articles on the use of ^{11}C- or ^{18}F-choline PET or PET/CT in brain tumours. The first step involved a search algorithm based on the combination of the Mesh terms: ''positron emission tomography'', ''choline'', and ''brain neoplasm''. No beginning date limit was used and the search was updated until April 30, 2016. To expand the search, our second step was to screen the references of retrieved articles, including any additional studies providing relevant information about the topic.

All studies investigating the clinical applications of ^{11}C- or ^{18}F-choline in brain tumours were eligible for inclusion. The exclusion criteria were: articles not within the field of interest of this review; review articles, editorials, letters, or comments; case reports or case series with less than ten patients; and publication language other than English, Spanish, or French.

Two researchers (NT and ET) independently reviewed the titles and abstracts of the retrieved articles, applying the inclusion criteria. The same two researchers then independently reviewed the full-text version to confirm their eligibility for inclusion. Disagreements were resolved with the help of a third researcher (MG). For each included study, information was collected concerning the article (author names, journal, year of publication, and country of origin), the study (objectives, design, results, and confirmation), patient characteristics (number of patients and type of tumours evaluated), and PET tracers used (^{11}C- or ^{18}F-choline and others). The studies were classified according to the Oxford Centre for Evidence Based Medicine (OCEBM) level of evidence [44]. For the analysis of each selected study, we intended to obtain: the main variables, sensitivity (SE), and specificity (SP).

To a better understanding for the lector, each publication will be explained in the clinical application that it refers to and in a chronological sequence.

Results

In the first step, 36 publications matched the proposed Mesh terms. After the second step search, a total of 85 articles were found. Afterwards, 70 publications have been excluded, because of the following reasons: review articles (22); less than 10 patients (20); letters or commentaries (4); not the topic of interest (4); preclinical studies (14); and language: Chinese (1), Italian (1); and Russian (1). When there were two publications from the same working group with potentially overlapping patients, we decided to keep the one providing better details about the selected patients and/or a higher number of patients, consequently, excluding [41, 45, 46] and including [42, 47, 48]. There were only 15 studies of more than ten patients fulfilling our criteria a priori to be included in a systematic review (Fig. 1; Table 1).

Diagnosis and tumour characterization

The first series of patients, including only suspected brain tumours, was reported by Ohtani et al. [49], comparing ^{11}C-choline-PET (^{11}C-CHO-PET), contrast enhanced MRI, and ^{18}F-FDG-PET in a prospective series of 22 patients, all with the histologic analysis of the lesion. Measures of the choline uptake by SUV and the tumour-to-normal-white-matter ratio (T/N) were determined in all lesions, and were increased in nine patients with high-grade glioma (HGG). These results showed that there was a correlation between the uptake and the histological tumour grade (higher in high-grade), then allowing their differentiation from low-grade gliomas (LGG). However, in the LGG (six patients), ^{11}C-choline uptake was low in four; therefore, it could not differentiate between low-grade gliomas and benign lesions. In five HGG patients, there was evidence of choline uptake in non-enhanced MRI area, and subsequently, the authors suggest the combination of ^{11}C-CHO-PET and MRI to improve the tumour delineation [49].

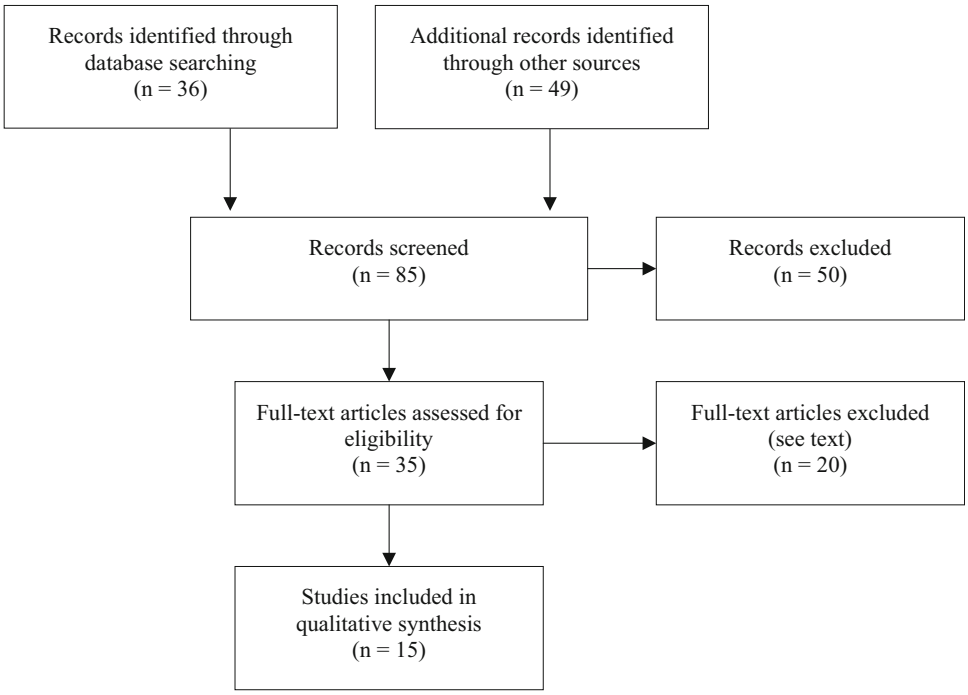

Fig. 1 Flow chart of the search for eligible studies

In 2003, Utriainen et al. [50] performed a prospective case–control study of 12 patients with suspected brain tumour who underwent MRS and ^{11}C-CHO-PET. Final diagnosis was established by histologic confirmation. In their study, ^{11}C-CHO-PET did not show any uptake in the benign lesions ($n = 2$), neither in 3/5 LGG. ^{11}C-CHO-PET was positive in two LGG and in all HGG ($n = 3$) and lymphoma ($n = 2$). The authors also observed a positive correlation between ^{11}C-CHO-PET uptake and Ki-67 proliferation index [50].

In the same year, Hara et al. [51] compared the performance of both ^{11}C-choline and ^{18}F-choline PET in 12 patients with untreated gliomas. In agreement with the previous reports, both tracers showed high uptake in all HGG ($n = 9$) allowing their differentiation from LGG ($n = 3$), in which one oligodendroglioma was negative. The authors concluded that both radiopharmaceuticals were adequate for the delineation and characterization of primary brain tumours, showing ^{18}F-choline a slightly higher tumour-to-normal (T/N) brain tissue uptake ratio than the ^{11}C-choline [51].

Tian et al. [47], in a prospective series, including 25 brain lesions (16 gliomas), assessed the usefulness of ^{11}C-CHO-PET respect to FDG-PET for the differentiation between benign and malignant brain tumours. They reported a significant difference in the mean SUV between benign and malignant lesions, with global accuracy of 58 % for FDG and 79 % for ^{11}C-choline. ^{11}C-CHO-PET showed highest contrast than FDG-PET in the brain, supporting its use in brain tumours. The details about histological characterization are not provided to analyze each subgroup according to tumour aggressiveness; nevertheless, the authors affirm that there are no differences in the intensity of ^{11}C-CHO-PET uptake between LGG and benign lesions. They suggest that attention needs to be drawn to the high uptake of ^{11}C-CHO-PET in some benign tumours and tumour-like lesions, as this will be of significance in clinical practice [47].

In 2007, Kwee et al. [15] studied ^{18}F-fluorocholine PET/CT (^{18}F-FCH-PET), a consecutive series of 30 patients with solitary brain lesions enhancing at MRI (in a mixed population of treated and untreated patients). When analyzing only the 16 untreated patients (six HGG, four benign lesions, and three metastasis), the authors observed that benign lesions have a low uptake opposed to the HGG and metastasis, with the highest uptake. Then, in agreement with the previous reports, ^{18}F-FCH-PET can aid in distinguishing benign lesions from malignant high aggressive lesions. Unfortunately, there were no low-grade gliomas in this group. Another interesting observation by Kwee is that in all glioblastoma multiforme (GBM) and one anaplastic oligodendroglioma (5/6 HGG), there was an increased uptake in the oedema around the lesion, in a non-enhanced MRI area, which potentially yields information about peritumoural involvement providing a value information for a better tumour delineation [15].

Kato et al. [52] assessed, by PET, the metabolic activity of 95 patients with untreated glioma (37 grade II; 37 grade III; and 21 grade IV) comparing ^{11}C-methionine, ^{18}F-FDG, and ^{11}C-choline, correlating metabolic activity to histopathological characteristics. All tracers showed significant positive correlations between their uptake and

Table 1 Systematic review included studies characteristics

Authors	Year	Journal	Country	Design	$n = 453$	Type of tumour		PET tracer	Confirmation: pathological (AP)/ other	Results/conclusions	Evidence level
Shinoura [48]	1997	Radiology	Japan	Case series	20	6 HGG; 3 metastasis 3 pituitary adenoma 3 meningioma 1 medulloblastoma	1 Hemangioblastoma 1 neurinoma 1Craniopharyngioma 1 lymphoma 12/20 post-treatment	^{11}C-CHO	16 AP 4 follow-up	^{11}C-CHO PET (+), potentially useful in distinguishing residual tumour from post-treatment changes	4
Ohtani [49]	2001	Eur J Nucl Med	Japan	Prospective and consecutive case series. Blinded	22	6 LGG 9 HGG 5 extra-axial tumours	2 Non-neoplastic All untreated	^{11}C-CHO ^{18}F-FDG	All AP	^{11}C-CHO PET enables differentiate LGG and HGG but not LGG from non-neoplastic lesions	2b
Utriainen [50]	2003	Journal of Neuro-Oncology	Finland	Prospective case series. Patients with suspicion of brain tumour. Blinded	12	1 Non-tumor lesion 1 Demyelinizating disease 4 Astrocytoma gr II 1 Oligoastrocytoma	2 Astrocytoma gr III 1 Glioblastoma multiforme 2 Metastasis All untreated	^{11}C-CHO	All AP	^{11}C-CHO PET was useful to differentiate benign/malign, but not to estimate glioma grade	2b
Hara [51]	2003	Journal of Neurosurgery	Japan	Prospective non consecutive case series. Blinded	12	2 Oligodendrogliomas 1 astrocytoma	2 Anaplastic astrocytoma 7 GBM All untreated	^{11}C-CHO ^{18}F-FCH	All AP	PET choline was useful to guide stereotactic biopsy. ^{18}F-FCH showed a slightly higher T/N ratio than ^{11}C-CHO choline	3b
Tian [47]	2004	Eur J Nucl Med	Japan	Prospective and consecutive case series. Not blinded	25	8 Astrocytoma 1 Ganglioglioma 1 Ependymoma 1 Oligodendroglioma 2 Neurocytoma 5 Glioblastoma glioneuronal lesion	1 Solitary fibrous tumor 1 Meningioma 1 Schwannoma 1Craniopharyngioma 1Malignant Lymphoma 1 Rathke's cleft cys 1 Dysplastic All untreated	^{11}C-CHO ^{18}F-FDG	All AP	Higher uptake in malign lesions. ^{11}C-CHO PET was useful for differentiation between malignant and benign tumours	3b

Table 1 continued

Authors	Year	Journal	Country	Design	$n = 453$	Type of tumour		PET tracer	Confirmation: pathological (AP)/ other	Results/conclusions	Evidence level
Kwee [58]	2007	Radiology	USA	Prospective and consecutive case series. Blinded	30	8 Metastasis 13 primary brain tumors: 7 GBM 1 Anaplastic astrocytoma 1 Anaplastic oligodendroglioma	3 Astrocytoma 1 Oligodendroglioma 9 benign: 5 demyelinating disease 4 radiation necrosis 16/30 Untreated	^{18}F-FCH	Malignant:AP Benigns: follow-up (6–27 months) in 6/9 and AP 3/9	^{18}F-FCH PET may aid in the differentiation of benign brain lesions, brain metastases, and high-grade gliomas. Also usefull for differential diagnosis recurrence/ radionecrosis	2b
Kato [52]	2008	AJNR	Japan	Prospective and consecutive case series	95 Gliomas	37 Grade II: 14 Diffuse astrocytoma 9 Oligodendroglioma 14 Oligoastrocytoma 37 grade III: 19 Anaplastic astrocytoma	13 Anaplastic oligodendroglioma 5 Anaplastic oligoastrocytoma 21 grade IV GBM All untreated	^{11}C-CHO ^{11}C-MET ^{18}F-FDG	All AP	^{11}C-CHO PET useful in evaluating the potential malignancy of oligodendroglial tumours	2b
Takenaka [53]	2011	Brain Tumor Pathol	Japan	Case series	46	6 Inflammatory (MAID: monofocal accute inflammatory demyelination)	19 Anaplastic astrocytoma 21 GBM All HGG treated	^{11}C-CHO ^{11}C-MET ^{18}F-FDG	45/46 AP	Higher^{11}C -CHO uptake in malignant gliomas	4
Tan [60]	2011	Clin Nucl Med	China	Prospective case series	55	37 Gliomas 1 brain neuroblastoma 1 brain lymphoma	1 Brain germinoma 15 metastasis All treated	^{11}C-CHO ^{18}F-FDG	39 Malignant (16 AP; 23 follow-up) 16 benign (5 AP; 11 follow-up > 11 months)	^{11}C-CHO with higher SE and SP may be better in distinguishing recurrent brain tumor from radiation necrosis compared with^{18}F-FDG PET/CT and MRI	2b

Table 1 continued

Authors	Year	Journal	Country	Design	$n = 453$	Type of tumour		PET tracer	Confirmation: pathological (AP)/ other	Results/conclusions	Evidence level
Li [59]	2012	Nuclear Medicine and Biology	China	Prospective case series	16	5 Grade II 7 grade III 4 grade IV	Post-surgical HGG pre-RT	^{11}C-CHO	Follow-up (9–30 months)	Difference in MRI and ^{11}C-CHO PET volumes. Changes in GTV in 5/16 patients. ^{11}C-CHO PET delineates GTV more accurately; larger series needed	3b
Mertens [42]	2012	Nucl Med Comm	Belgium	Prospective series	24 (25 lesions)	11 Glioblastoma 3 Anaplastic astrocytoma 2 Oligoastrocytoma 1 Pilocytic astrocytoma 1 Meningothelial meningioma 2 Meningioma (MRi)	1 Mixed-type angiomatous (grade 1) and clear cell meningioma (grade 2) 2 Radiation necrosis (MRi) 1 Tumefactive demyelinating lesion 1 Metastasis All untreated	^{18}F-FCH	21 AP 3 imaging (MRI)	^{18}F-FCH PET is useful for the detection of brain tumours and other brain lesions	2b
Li [61]	2014	Tumor Biology	China	Prospective cohort	16	7 Grade III: 2 Anaplastic astrocytoma 5 Oligodendroglioma 9 grade IV	8 GBM 1 Giant cell glioblastoma All previously treated HGG suspicious for relapse	^{11}C-CHO	3 AP 13 follow up (3.8–24 months)	^{11}C-CHO PET/CT had high SE for the differential diagnosis of recurrence/RN. Preliminary results suggest that ^{11}C-CHO T/N ratio is a predictor of survival in patients with suspected recurrent HGG	2b

Table 1 continued

Authors	Year	Journal	Country	Design	$n = 453$	Type of tumour		PET tracer	Confirmation: pathological (AP)/ other	Results/conclusions	Evidence level
Takenaka [62]	2014	Neurol Med Chir	Japan	Retrospective review of a prospective cohort	50	17 Grade III: 7 Anaplastic astrocytomas 10 Anaplastic oligodendrogliomas	17 Grade IV GBM 16 radiation necrosis All post-treated (radiotherapy) HGG	^{11}C-CHO ^{11}C-MET ^{18}F-FDG	All AP	Diagnostic accuracy CHO: SE 73.5 %, SP 87.5 %; MET SE 91.2 %, SP: 87.5 %; FDG SE 76.5 %, SP 75.0 % MET PET superior to both CHO and FDG in diagnostic accuracy for distinguishing glioma recurrence from RN	2b
Fraioli [54]	2015	Clin Nucl Med	UK	Case series	12	8 LGG 4 HGG	All untreated	^{18}F-FCH	All AP	^{18}F-FCH is useful for diagnosis and response assessment	4
Gómez-Río [63]	2015	Eur J Nucl Med	Spain	Prospective cohort	18	6 Diffuse astrocytoma 2 Diffuse fibrillary astrocitoma 2 Oligoastrocytoma 5 Oligodendroglioma	1 Ependymoma 4th ventricle 1 Ganglioglioma 1 LGG All post-treated LGG	^{18}F-FCH	5 AP 13 consensus neuro-oncology group	^{18}F-FCH PET/CT superior than aMRI and ^{201}Tl-SPECT for differential diagnosis of recurrence/RN. Global diagnostic accuracies: 90.9 % aMRI; 69.2 % ^{201}Tl-SPECT and 100 % ^{18}F-FCH PET/CT; high clinical impact	3b

LGG low-grade glioma, *HGG* high-grade glioma, *AP* pathological confirmation, *SE* sensitivity, *SP* specificity, *RN* radiation necrosis

tumour grade in astrocytic tumours. Summarizing, the highest intensity of uptake of ^{11}C-choline corresponded to grade IV glioma, higher than grade III, which, in turn, was higher than the LGG that had already a significant uptake. In the subgroup of astrocytic tumours, the best performance was for ^{11}C-methionine in the evaluation of localization, grade, type, and proliferative activity. However, in oligodendroglial subtype, a positive correlation was found between ^{11}C-CHO-PET uptake and tumour grade. Afterwards, ^{11}C-CHO-PET is recommended for the evaluation of this type of tumours [52].

Takenaka et al. [53] evaluated a series of 46 patients. They all underwent MRS and PET with ^{11}C-choline, ^{11}C-methionine, and ^{18}F-FDG, with posterior pathological confirmation except in one patient. Final diagnosis was anaplastic astrocytoma (AA) in 19 patients; GBM in 21; and monofocal acute inflammatory demyelination (MAID) in 6 patients. They observed that the MRS Cho/Cr ratio, the MET-PET T/N ratio, and the ^{11}C-CHO-PET T/N ratio of MAID were significantly lower than that of AA and GBM. On this basis, they concluded that combined PET and MRS neuroimaging examinations may be useful for distinguishing MAID from malignant gliomas, but no LGG were included [53].

In 2012, Mertens et al. [42] prospectively performed ^{18}F-FCH-PET in 24 patients with 25 space-occupying lesions in the brain. Final diagnoses were determined by pathology (21 patients), or MRI and follow-up (three patients), including: eleven GBM, three anaplastic astrocytoma, two oligoastrocytoma, one pilocytic astrocytoma, four meningiomas, one metastasis, one tumefactive demyelinating lesion, and two radiation necrosis. These authors reported an increased uptake of ^{18}F-FCH-PET in all malignant high-grade ($n = 14$) and low-grade lesions ($n = 3$; 2/3 with contrast-enhancement) and also in seven non-tumoral lesions. They proposed that the performance of a dynamic acquisition enables to differentiate the uptake kinetics of the tracer to have a better accuracy in the differential diagnosis, especially for brain meningiomas [42].

In pediatric patients, Fraioli et al. [54] evaluated the role of ^{18}F-FCH PET/MRI in 12 histologically proven astrocytic brain tumours (4 HGG and 8 LGG). All patients had a significant FCH uptake, which matched the areas of contrast enhancement and restricted diffusion. There was a negative correlation trend between SUVmax and ADCmean and a positive correlation trend between SUVmax and tumour size. All tumours had an increased FCH uptake that, independent from its grade and, surprisingly, LGG had a wide range of uptake, some of them even higher than HGG, as set above, coincident with contrast-enhanced areas in MRI in all the cases [54].

As the previously mentioned, publications have heterogeneous population with different inclusion criteria and divers tumours, it was not possible to perform a statistical analysis comparing them according to the systematic review methodology [55]. However, to a better understanding, a synthesis of the above information is available (Table 2), including only untreated patients with pathologically confirmed lesions. All the HGG ($n = 150$) were positive with PET-CHO, and in general, there is a trend to have a higher uptake in more aggressive lesions, making its diagnosis easier. On the opposite, for LGG, PET-CHO was positive in 54/62 and falsely negative in 8/62. This finding has already been reported by Roelcke [56] in a small series of six pre-operative-confirmed LGG patients that were negative in both: ^{18}F-FCH-PET and ^{18}F-FET-PET. As a consequence, LGG diagnosis and characterization are less evident by ^{18}F-FCH-PET. There are not any specific publications addressing to the relation of FCH uptake and the enhanced areas in MRI; there are reported cases of increased FCH uptake without enhanced effect mostly in LGG [41, 51, 52], while, in untreated HGG, the most frequent observation is an increased uptake topographically coincident with MRI contrast-enhanced areas [49, 51–53, 58]. In benign lesions, PET-CHO was negative in 7/18 and positive in 11/18; subsequently, it did not allow a trusting differentiation with PET-CHO positive LGG. Other authors [57] have reviewed, in 110 PET studies, the misdiagnoses of ^{11}C-CHO-PET, finding five false positives corresponding to inflammatory lesions as demyelination, abscess, and brain granuloma. Therefore, attention needs to be drawn in the interpretation in the presence of a focal brain uptake, needing a complimentary MRI and detailed clinical information.

Guide for biopsy

Hara et al. [51] performed ^{18}F-choline and ^{11}C-choline PET in 12 patients with suspected glioma, prior to stereotactic biopsy. Biopsies were performed in the area with highest uptake, being all positive for the glioma diagnosis, including nine HGG and three LGG. In 9/12 patients, choline uptake was coincident with MRI contrast-enhancement; while in two patients (one HGG and one LGG), there was choline uptake in non-enhanced MRI areas, consequently, improving the tumour delineation for directing the biopsy. Then, the authors concluded that ^{18}F-choline and ^{11}C-choline PET are both useful tools to determine the most appropriate target for sampling [51].

Other authors in different studies for which the biopsy target is not the main objective also mention the value of PET-CHO for this clinical indication [50, 58]. Kwee underlines the fact that HGG have a characteristic uptake outside the margins of the contrast-enhanced area; in two

Table 2 ^{11}C-CHO-PET and ^{18}F-FCH-PET for characterisation of untreated brain lesions with posterior histopathological confirmation

Authors	Year	Total patients $n = 257$	Total HGG $n = 150$	HGG PET (+) $n = 150$	Total LGG $n = 62$	LGG PET (+) $n = 54$	LGG PET (−) $n = 8$	Total Benign lesions $n = 18$	Benign lesions PET (+) $n = 11$	Observations
Shinoura [48]	1997	4	2	2	0	0	0	2	2	Mixed series, all (+)[a]
Ohtani [49]	2001	22	9	9	6	2	4	2	0	Primary diagnosis[a]
Utriainen [50]	2003	12	3	3	5	2	3	2	0	Primary diagnosis[a]
Hara [51]	2003	12	9	9	3	2	1	0	0	Primary diagnosis[a]
Tian [47]	2004	25	5	5	11[c]	N/A	N/A	5[c]	N/A	Mixed series[a]
Kwee [58]	2007	9	6	6	0	0	0	3	0	Mixed series[b]
Kato [52]	2008	95	58	58	37	37	0	0	0	Primary diagnosis, all (+)[a]
Takenaka [53]	2011	45	40	40	0	0	0	5	5	Primary diagnosis. All (+) but benign had lower uptake[a]
Mertens [42]	2012	21	14	14	3	3	0	4	4	Primary diagnosis. All (+); different kinetics of meningiomas[b]
Fraioli [54]	2015	12	4	4	8	8	0	0	0	Primary diagnosis in pediatrics, all (+)[b]

Positive (+) and negative (−) PET-choline uptakes according to each article. Sensitivity: 100 % in high-grade glioma (HGG) and 87 % in low-grade glioma (LGG)

[a] ^{11}C-CHO-PET

[b] ^{18}F-FCH-PET

[c] Excluded for the analysis, because the information was not available (N/A)

cases of its series, the diagnosis was made from a stereotactic biopsy of the peri-tumoral region [58].

Treatment planning: radiosurgery and radiotherapy

In 2012, Li et al. [59] explored the clinical value of ^{11}C-CHO-PET in the optimization of target volume delineation and treatment regimens in a prospective cohort of 16 previously resected gliomas (grade II, III, and IV) prior to radiotherapy. The tumour target volume was determined by both MRI and ^{11}C-CHO-PET. In ^{11}C-CHO-PET, the tumour target volume, corresponding to the highly metabolic area, was well contrasted and better defined compared to MRI. The radiotherapy target volumes were changed for 31.3 % (5/16) of patients based on the ^{11}C-CHO-PET uptake. According to the tumour histology, the change rate was 80 % (4/5), 14.3 % (1/7), and 0 % (0/4) for patients with WHO grades II, III, and IV gliomas, respectively. Therefore, these authors concluded that ^{11}C-CHO-PET is a complimentary diagnostic approach to MRI allowing a more accurate definition of target volumes for the radiation therapy for primary brain tumours [59] (Fig. 2).

Follow-up glioma: differential diagnosis of recurrence/radionecrosis

Shinoura et al. [48], in 1997, were the first to report a series of 20 brain tumour patients, imaged with ^{11}C-CHO-PET. In this series, there were 11/20 patients previously treated by cranial irradiation, showing a decrease of ^{11}C-choline uptake in accordance with a clinical improvement, highlighting the value of ^{11}C-CHO-PET for differentiating residual tumour tissue from post-treatment changes. In this series, there was no LGG [48], and in 19/20 patients, choline uptake matched MRI contrast-enhanced areas.

In the previously referred series of Kwee et al. [58], 14 patients had previously undergone radiation therapy (ten HGG and four metastases). In the areas of high ^{18}F-FCH-PET uptake it was possible to detect recurrence, that was histopathologically confirmed in nine patients. In the remaining five patients with low ^{18}F-FCH-PET uptake, a 1-year follow-up showed no progression, in agreement with the diagnosis of radiation necrosis [58].

In 2011, Tan et al. [60] analyzed a prospective series of 55 patients with treated brain tumours (15 metastasis, 1 germinoma, 1 neuroblastoma, 1 lymphoma, and 37 gliomas) under follow-up and suspicion of relapse. They aimed

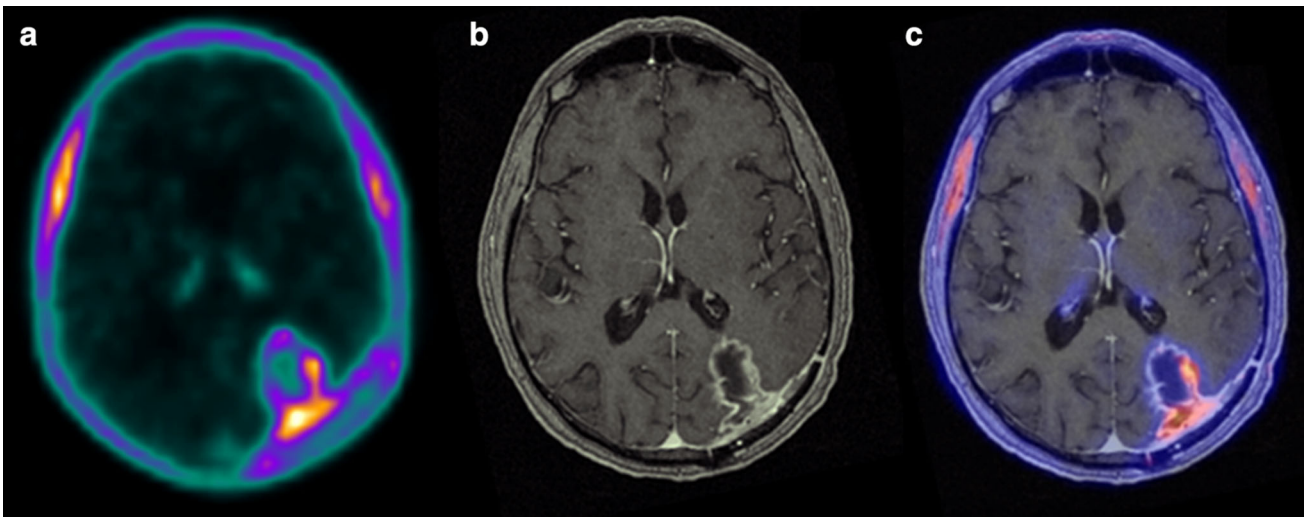

Fig. 2 FCH-PET/CT (**a**), Gd-T1-MRI (**b**), and PET + MRI superposition (**c**) of ^{18}F-fluorocholine PET/CT and Gd-MRI of a patient diagnosed of GBM after surgical resection. FCH-PET/CT was performed prior radiotherapy for the evaluation of residual tumour activity showing heterogeneous uptake in the margins of the enhanced area at left parieto-occipital lobe

to compare the accuracy of MRI, FDG PET/CT, and ^{11}C-Choline PET/CT for the differentiation of tumour recurrence from radiation necrosis. The results of the imaging techniques were compared to pathology (21 patients) or an 11-month follow-up, considering radiation injury if a lesion became smaller in size. The final diagnosis based on these criteria was: tumour recurrence in 39 patients and radiation injury in 16. The sensitivities of MRI, FDG-PET/CT, and ^{11}C-CHO-PET/CT in lesion diagnosis were 87.2, 76.9, and 92.3 %, respectively, and their specificities were 81.3, 62.5, and 87.5 %, respectively. They concluded that ^{11}C-CHO-PET/CT with higher sensitivity (SE) and specificity (SP) may be better in distinguishing recurrent brain tumour from radiation necrosis compared with FDG-PET/CT and MRI [60].

In 2014, Li et al. [61] evaluated the role of ^{11}C-CHO PET/CT in detecting tumour recurrence in patients with post-treated HGG. A prospective cohort of 16 previously treated histopathologically proved that grade III ($n = 7$) and grade IV ($n = 9$) glioma patients with suspicion of relapse were included. The final diagnosis of patients was established by histological confirmation in only three patients; in the remaining 13 patients, the final result was achieved based on a clinical and imaging follow-up (3.8–24 months, mean: 12.3). According to that, the authors determined for ^{11}C-CHO-PET/CT SE: 100 %, SP: 70 %, whereas Gd-MRI was SE: 83.3 %, SP: 60 %. ^{11}C-CHO-PET/CT was best when analyzing the area under the ROC curve of the T/N ratio, establishing a cut-off value of 1.42 with an accuracy of 93.8 % [61].

In 2014, Takenaka et al. [62] performed a retrospective review of a consecutive recruited 50 patients with histological diagnosis of HGG already treated by surgery plus radiotherapy with suspicion of relapse. All patients underwent imaging evaluation with ^{11}C-MET-PET, ^{11}C-CHO-PET, ^{18}F-FDG-PET, and MRI performed in a single day. The imaging results were compared to the confirmed histopathological results that revealed the presence of 7 anaplastic astrocytomas, 10 anaplastic oligodendrogliomas, 17 GBM, and 16 radiation necrosis. Measures were performed to calculate the PET/Gd volume ratio, the PET/Gd overlap ratio, and the T/N ratio, and determine the optimal index of each PET scan. The PET/Gd volume ratio and the PET/Gd overlap ratio for radiation injury were significantly lower than those of glioma recurrence only with ^{11}C-MET-PET. The T/N ratio of radiation necrosis was significantly lower than that of GBM with all PET imaging and was significantly lower than that of grade III tumours, especially for anaplastic oligodendrogliomas, only with ^{11}C-MET-PET images. Receiver-operating characteristic (ROC) analysis showed the following values for each procedure: ^{11}C-MET-PET: area under the curve (AUC): 0.925; cut-off value for tumour: 2.51 (SE 91.2 % SP 87.5 %); ^{11}C-CHO-PET: AUC: 0.814; cut-off value for tumour: 8.92 (SE 73.5 % SP 87.5 %), and ^{18}F-FDG-PET: AUC: 0.774; cut-off value for tumour: 1.26; (SE 76.5 % SP 75 %). These results suggested that the global accuracy for ^{11}C-MET-PET was superior to both ^{11}C-CHO-PET and ^{18}F-FDG-PET. ^{11}C-CHO-PET had lower sensitivity, but the same specificity of ^{11}C-MET-PET for distinguishing glioma recurrence from radiation necrosis [62].

Gómez-Río et al. [63], in 2015, prospectively evaluated the role of ^{18}F-FCH-PET/CT specifically in the follow-up of LGG. They included 18 post-treated LGG

patients under standard follow-up with indeterminate clinical and/or radiological findings of tumour activity. All patients underwent clinical evaluation, aMRI, ^{201}Tl-SPECT, and ^{18}F-FCH-PET/CT. The final diagnosis was established by histology (6 patients) or by consensus of the Neuro-oncology Group (12 patients) after a follow-up >6 months. According to that, the global diagnostic accuracies were 90.9 % for aMRI (38.8 % inconclusive), 69.2 % for ^{201}Tl-SPECT (11.1 % inconclusive), and 100 % for ^{18}F-FCH-PET/CT. The use of ^{18}F-FCH-PET/CT led correctly to a change in the approach suggested by routine follow-up in 72.2 % of patients and endorsed it in the remaining 27.8 %. The authors concluded that structural MRI needs complementary metabolic imaging with aMRI and nuclear medicine procedures in selected patients. ^{18}F-FCH-PET/CT can be useful in the individualized management of patients with treated LGG with uncertain clinical and/or radiological evidence of tumour activity [63].

The available evidence about this clinical indication is very heterogeneous, not allowing a comparison between studies (Table 3). Few authors did not specify each patient's characteristic [60] and outcome [48], probably, because it was not part of their main objectives. Another problem found was the lack of pathological analysis (AP) as a gold standard to compare the PET-CHO results, especially in the LGG patients, where the final diagnosis was established mostly by follow-up and MRI.

On the other side, for HGG, all except three were histologically confirmed of tumour recurrence, probably because the aggressiveness of the neoplasm forced a surgical intervention; then, in this setting, PET-CHO showed SE 75 % and SP 83 % (Table 4).

In summary, despite the heterogeneous pool of patients, in all studies, PET-CHO showed a high accuracy in the differential diagnosis between tumour recurrence and radiation necrosis, being a promising non-invasive tool in neuroimaging for this indication.

Table 3 ^{11}C-CHO-PET and ^{18}F-FCH-PET in post-treated gliomas, for differential diagnosis between tumour recurrence and radiation necrosis (RN)

Authors	Year	Total patients	Primary HGG	Recurrent HGG	Primary LGG	Recurrent LGG	Suspected RN	Confirmed RN	Comments/follow-up (mean)
Kwee [58]	2007	10	9	7	1	0	3	3	All pathologically confirmed[b]
Tan [60]	2011	37[c]	N/A	10[c]	N/A	1[c]	16[c]	5[c]	11 months[a]
Li [61]	2014	16	16	6	0	0	10	0	12.3 months[a]
Takenaka [62]	2014	50	50	34	0	0	16	16	All pathologically confirmed[a]
Gómez-Río [63]	2015	18	0	0	15	6	3	0	>6 months[b]

HGG high-grade glioma, *LGG* low-grade glioma

[a] ^{11}C-CHO-PET

[b] ^{18}F-FCH-PET

[c] Excluded for the analysis, because the information was not available (N/A)

Table 4 Diagnostic accuracy of ^{11}C-CHO-PET and ^{18}F-FCH-PET in post-treated high-grade gliomas (HGG), for differential diagnosis between tumour recurrence (Rec) and radiation necrosis (RN)

Authors	Year	Total patients	Rec HGG	AP Rec HGG	RN	AP RN	PET positive	True positive	Comments/follow-up (mean)
Kwee [58]	2007	9	7	7	2	2	7	7	All AP confirmed[b]
Li [61]	2014	16	6	3	10	0	9	6	12.3 months[a]
Takenaka [62]	2014	50	34	34	16	16	27	25	All AP confirmed[a]
		75	47	44	28	18	43	38	

When considering only pathologically (AP) confirmed patients ($n = 62$), *SE* 75 % and *SP* 83 %. When also including follow-up for definitive diagnosis ($n = 75$), *SE* 81 % and *SP* 82 %

[a] ^{11}C-CHO-PET

[b] ^{18}F-FCH-PET

Response assessment

Even though many authors have mentioned this topic, there are no studies specifically aiming to evaluate the treatment response assessment of brain tumours by PET-CHO in adults. Recently and only the paper of Fraioli et al. [54] intended to evaluate the role of ^{18}F-FCH-PET/MRI in histologically proven astrocytic brain tumours. A prospective series of 12 pediatric astrocytic brain tumours (eight LGG and four HGG) was included; 10/12 had a baseline exploration that was lately compared to the post-treatment study. There was concordance between reduction in tumour size and reductions in SUVmax and SUVmean in four children, in three of whom ADCmean values were increased. In two patients, tumour size remained stable, whereas SUVmax and SUVmean values were increased with reduction in the ADCmean values. In addition, in two children, cross-sectional studies showed an increase in tumour size and SUVmax, but a reduction in ADC values. The authors concluded that simultaneous ^{18}F-FCH-PET/MRI is a promising and reliable imaging tool for children with astrocytic tumours, as it permits monitoring of morphological and metabolic response and changes during therapy [54].

Prognosis

In a previously mentioned work from 2014, Li et al. [61] evaluated the role of ^{11}C-CHO-PET/CT in detecting tumour recurrence and predicting survival in patients with post-treated HGG. In this prospective cohort of 16 previously treated grade III ($n = 7$) and grade IV ($n = 9$), glioma patients with suspicion of relapse ^{11}C-CHO-PET/CT showed higher accuracy than MRI to detect tumour recurrence. Moreover, these authors evaluated if there is a relationship between ^{11}C-CHO-PET/CT uptake and patients prognosis. The Cox regression analysis found that there was correlation of ^{11}C-CHO-PET/CT T/N ratio with overall survival, independent of Karnofsky performance score. Patients with lower T/N ratio ($\leq$1.42) had longer survival than patients with higher T/N ratio, considering both, progression-free and overall survival [61].

Other applications

The lack of scientific evidence prevents us to include the following applications in this intended systematic review. However, we considered that it was important to mention them, because they may represent near future indications for brain imaging with PET-CHO.

Meningiomas

Meningiomas are very frequent, typically slow-growing and usually histopathologically benign. Only one published study by Giovacchini et al. in 2009 addressed specifically these lesions [64]. It aimed to compare both ^{18}F-FDG uptake and ^{11}C-CHO uptake in seven histologically confirmed untreated meningiomas (pre-surgical). All the lesions had an increased uptake of ^{11}C-CHO, whereas ^{18}F-FDG was decreased in six patients. Then, ^{11}C-CHO-PET/CT provided excellent visualization of all meningiomas and higher uptake in grade II (2/7) than grade I (5/7), having potentially the ability for grading them. ^{11}C-CHO-PET/CT provided an optimal delineation of meningiomas that could be clinically relevant in the integration of PET and CT information for planning stereotactic radiotherapy and, also, for monitoring the response to treatment; although more studies with a greater number of participants are needed to confirm these findings. Mertens et al. [42] suggested that an early (5–10 min) and delayed acquisition PET could be helpful to differentiate between meningioma and other brain tumours based on its quick uptake and subsequently decreasing activity.

Other authors performing PET-CHO in prostate cancer patients have reported intracranial high-choline uptake due to meningiomas [65–67]. In an effort to have a larger descriptive series, we included meningiomas from the previously included articles in this review and, also, case reports [68], having a total of 27 meningiomas visualized by PET-CHO, only 12 with histological confirmation (Table 5). No conclusions are intended to be drawn from this; we only aimed to note that brain meningiomas can be observed by PET-CHO.

Metastasis

The only specific study on brain metastases evaluated by PET-CHO was performed in 2011 by Rottenburger [69]. In a prospective series, the aim was to compare ^{11}C-methionine to ^{11}C-choline for imaging brain metastases in eight patients (seven treated and one untreated). The ^{11}C-choline had a better performance than the ^{11}C-methionine, with significantly higher lesion-to-normal-brain tissue ratio, without evidence for a lower specificity for ^{11}C-choline. Biopsies were performed, therefore, confirming the positive diagnoses of metastasis and the negatives, corresponding to radiation necrosis. This study revealed very promising results with the use of ^{11}C-choline for the evaluation of brain metastases in the planning of stereotactic biopsies to avoid false-negative biopsy results as well as their differential diagnosis between progression and radiation necrosis [69].

Other authors have also observed a high uptake of choline by brain metastasis (Table 6). The reported lesions

Table 5 Descriptive studies about ^{11}C-CHO-PET and ^{18}F-FCH-PET and suspected brain meningiomas by other imaging techniques, some of them pathologically confirmed

Authors	Year	Total patients	Suspected meningiomas[a]	Confirmed meningiomas[b]	PET tracer	PET result
Shinoura [48]	1997	20	3	1	^{11}C-CHO	(+)
Tian [47]	2004	81	1	1	^{11}C-CHO	(+)
Mertens [42]	2012	24	4	2	^{18}F-CHO	(+)
Giovacchini[c] [64]	2009	7	7	7	^{11}C-CHO	(+)
Fallanca[c] [65]	2009	402	4	1	^{11}C-CHO	(+)
Schillacci[c] [66]	2010	80	1	0	^{18}F-CHO	(+)
Bertagna[c] [68]	2013	1	1	0	^{11}C-CHO	(+)
Calabria[c] [67]	2014	300	6	0	^{18}F-CHO	(+)
		915	27	12		

(+): Positive choline uptake described by authors

[a] Suspected brain meningiomas by other imaging techniques

[b] Some of them pathologically confirmed

[c] Studies not included in the systematic review

Table 6 Studies of PET-CHO and pathologically proven brain metastases

Authors	Year	Total patients	Total metastasis	Untreated/treated	Radiotracer	Findings
Shinoura [48]	1997	20	1	Untreated	^{11}C-CHO	T/N 41.9
Utriainen [50]	2003	12	2	Untreated	^{11}C-CHO	SUV 3.5, 0.79
Kwee [58]	2007	30	3	2 Untreated 1 treated	^{18}F-FCH	1.2–2.28/4
Tan [60]	2011	55	15	Treated	^{11}C-CHO	Not provided
Rottenburger[a] [69]	2011	8	7	1 Untreated 7 treated	^{11}C-CHO	High uptake in all
Mertens [42]	2012	24	1	Untreated	^{18}F-FCH	T/N 4.53
Imperiale[a] [78]	2014	1	1	Untreated	^{18}F-FCH	SUV 7.3
		150	30			

[a] Studies not included in the systematic review

arise from very heterogeneous series with treated and untreated metastasis from different primary tumours, visualized either by ^{18}F-FCH or ^{11}C-CHO, which prevent us from further analysis. However, 30/32 metastasis had histopathological confirmation and all of them were well visualized by PET-CHO, which could be useful in oncology. Interestingly, Kwee et al. [58] observed that metastasis could be differentiated from HGG, because of their higher choline uptake and the absence of peri-tumoral uptake, characteristic of HGG.

Others

The very low brain uptake of choline makes it a suitable tracer for almost any brain lesion: malignant or benign. Only for illustrating this observation, several cases and small series have been reported in the last 5 years for the following: hemangioblastoma, hemangiopericytoma, gliosarcoma, pineal germ cell tumour, vascular lesion, non-germinomatous germ cell tumour, CNS primary NK-cell lymphoma, and primary diffuse leptomeningeal melanomatosis [70–77].

Conclusion

After this exhaustive and systematic review of the literature, the authors concluded that PET or PET/CT with radiolabelled ^{11}C or ^{18}F-choline must be considered as an emerging procedure for the evaluation of brain tumours. Most of the available evidence is about gliomas, but many other brain lesions have also been successfully imaged and reported, especially in the last 5 years.

We are in agreement with Treglia and Giovannini [79, 80] about the utility of PET-CHO to differentiate high-

grade glioma from low-grade glioma, to early detect brain tumour recurrence, to guide stereotactic biopsy sampling and to define radiation treatment targets; more recently, it has also been used for treatment response assessment and to estimate patients' prognosis. In all of the above-mentioned indications, PET-CHO was useful, because of its advantage in the brain of having low physiologic uptake, therefore, providing precise images with a very good tumour-to-background ratio in brain lesions. From a neuro-oncological point of view, in the critical scenario of having a patient with a suspected tumour recurrence, the need for a non-invasive diagnostic tool is a main priority. For the sake of the patient, all the efforts must be made to rapidly confirm and treat the tumour or rule it out, thus, having a direct clinical impact. PET-CHO showed high accuracy for these and other indications; however, the available evidence was not enough to confidently affirm its benefits over other best documented radiopharmaceuticals, although, other aspects must be considered in the current clinical practice, such as giving the patient access to the technique. Therefore, in neuro-oncology, in the absence of other tracers, how about trying PET choline?

Compliance with ethics standards

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Ethical standards This article does not contain any studies with human or animal subjects performed by the any of the authors.

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